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THE RELATION OF SO-CALLED BRILL'S DISEASE TO TYPHUS FEVER.

AN EXPERIMENTAL DEMONSTRATION OF THEIR IDENTITY.

By John F. Anderson, Director Hygienic Laboratory, and Joseph Goldberger, Passed
Assistant Surgeon.

Typhus fever has not appeared in epidemic form in the United States since the comparatively small outbreaks in New York in 1891-92 and in Philadelphia in 1883. Sporadic cases have been reported, as the 4 cases in Baltimore in 1901 and occasional cases among recently arrived immigrants. It has been a subject of speculation among health authorities why, in spite of the arrival of occasional cases in this country and of many persons from endemic foci of the disease, typhus fever apparently does not gain a foothold in the United States. It will be shown later that such a possibility is not without reason, and that the disease is actually present at all times in certain cities of the United States.

In 1898 Dr. Nathan E. Brill,¹ of New York, reported 17 cases of a disease clinically resembling typhoid fever but without the Widal reaction, and clearly set forth the differences between this group and the usual types of typhoid fever cases.

In April, 1910, he reported in a most interesting paper² a study of 221 cases of the same disease observed at Mount Sinai Hospital, New York City, from late in 1896 to December 1, 1909.

Since the important features of the disease as observed by him are well summed up in his definition, it is given:

An acute infectious disease of unknown origin and unknown pathology, characterized by a short incubation period (four to five days), a period of continuous fever, accompanied by intense headache, apathy, and prostration, a profuse and extensive erythematous maculo-papular eruption, all of about two weeks' duration, whereupon the fever abruptly ceases either by crisis within a few hours or by rapid lysis within three days, when all symptoms disappear.

In a third paper Brill³ reports on the study of 34 additional cases observed since the 221 previously reported. It may be noted that

¹ Brill, Nathan E.: A study of 17 cases of a disease clinically resembling typhoid fever, but without the Widal reaction; together with a short review of the present status of the serodiagnosis of typhoid fever. N. Y. med. journ., vol. 67, Jan. 8 and 15, 1898, pp. 48 and 77.

² Brill, Nathan E.: An acute infectious disease of unknown origin. A clinical study based on 221 cases. Am. journ. med. sci., April, 1910.

³ Brill, Nathan E.: Pathological and experimental data derived from a further study of an acute infectious disease of unknown origin. Am. journ. med. sci., August, 1911.

these 34 cases all occurred in the year ended December 1, 1910, and in the same hospital, indicating an increasing prevalence of the infection or greater skill in diagnosis. This paper of Brill's is of especial interest and value because it includes, in addition to clinical data, the report of an autopsy on a fatal case and the results of the inoculation of monkeys with blood from two cases in the acute stage, and with the blood and emulsion of the liver and the spleen from the fatal case. Dr. Brill states that from the report of the autopsy "the conclusion may be drawn that the organs showed congestion and general parenchymatous degeneration such as would obtain in any intense infectious disease."

From material obtained at the autopsy, made about 18 hours after death, Brill inoculated three monkeys; one intravenously with 5 c. c. of heart's blood, one intraperitoneally with an emulsion of the liver, and one intraperitoneally with an emulsion of spleen. The animals were kept under observation for three months and showed no signs of illness.

Brill also reports inoculations with blood obtained during life. In one case 5 c. c. of blood was drawn from a patient in the seventh day of the disease and was inoculated subcutaneously and intraperitoneally into a *Macacus rhesus*; in a second instance 5 c. c. was drawn from a patient in the sixth day of the disease, diluted with 10 c. c. sodium citrate solution, and inoculated intravenously into a *semnopithecus*. The temperature of the first animal was taken for one month and of the second for three weeks. Both animals were kept under observation for two months, during which time they were entirely free from illness.

Brill states that this experimental work in inoculating monkeys has, at least so far, established a fundamental difference between the disease described by him and Mexican typhus fever sufficient, perhaps, to stamp them as separate diseases. He still reserves in his mind the belief that the disease may be due to an attenuated modification of the virus of typhus fever, and awaits the results of the further work of other investigators, although in a letter to the editor of the Journal of the American Medical Association¹ he apparently withdraws this reservation, as he states that he has in vain attempted to prove that it is typhus fever and shall regard it as such only when certain evidence set forth in his letter is produced and that until then he believes he is justified in calling this disease "an infectious disease of unknown origin."

Dr. Brill deserves the greatest credit for his careful study of the disease in question, and his ability as a close and careful observer is shown in first distinguishing cases of this disease, instances of which have almost certainly come under the observation of others.

Louria,² in a paper read before the Kings County Medical Society, reports the results of the observation of 18 cases in the Jewish Hospital, Brooklyn, N. Y., during the summer and fall of 1910.

Friedman,³ on clinical grounds, expresses the opinion that Brill's symptom complex is identical with mild and moderately severe cases of typhus fever.

¹ Journ. A. M. A., vol. 57, Dec. 2, 1911, p. 1854.

² Louria, Leon: Brill's disease. Med. rec., Aug. 26, 1911.

³ Friedman, G. A.: Brill's symptom complex; typhus fever; Manchurian typhus. Arch. internal med., vol. 8, Oct. 15, 1911, p. 427. Abst. Med. rec., vol. 80, Sept. 16, 1911, p. 606.

About the time that Brill's second paper appeared (April, 1910) we were engaged in the study of Mexican typhus fever¹ and, having the picture of that disease clearly in our minds, we were struck by the very marked clinical resemblance between it and the disease described by Brill. Influenced by this resemblance, we endeavored to obtain access to cases of Brill's disease in order to determine if possible the relationship between that infection and typhus fever. This we did not succeed in doing, however, until September, 1911.

Through the courtesy of Dr. Leo Kessel, New York, and of Dr. Olsan, house physician at Mount Sinai Hospital, New York, we had the privilege of seeing a case of Brill's disease in the wards of Mount Sinai Hospital on September 20, 1911. Chart No. 1 shows the temperature of this patient (case No. 1, N.²) from the day of his admission to the hospital to the day of his discharge. We shall not, at this time, go into the history of this patient beyond stating that he was in the seventh day of his illness when we first saw him, and that the case was considered by those familiar with Brill's disease to be a typical one of that disease.

Blood was drawn from the arm vein, defibrinated, and used for the inoculation of two rhesus monkeys (Nos. 149 and 150), each animal receiving 3 c. c. of the defibrinated blood intraperitoneally. The next day, in the eighth day of illness, blood was again drawn from an arm vein of this patient, defibrinated, and about three hours later was used for the inoculation of two rhesus monkeys (Nos. 151 and 152), each animal receiving approximately 3.5 c. c. of the blood, diluted with an equal volume of normal salt solution, intraperitoneally. Monkey No. 152 died 10 days later as a result of a purulent peritonitis, and monkey No. 151, which was in poor condition at the time of inoculation, and refusing food, continued progressively to fail. Six days later, being moribund, the animal was chloroformed.

Monkey No. 149, during a period of observation lasting 31 days, showed no evidence of illness, by rise of temperature or otherwise.

Ten days after inoculation the temperature of monkey No. 150 began to rise, reaching its maximum (41.2° C.) six days later. The temperature of the animal remained high until the eleventh day of fever, when it fell by rapid lysis, reaching normal 14 days after the rise began. On the sixth day of fever, when the temperature was at its maximum, 10 c. c. of blood were drawn from the animal's heart, defibrinated, and used for the inoculation of two rhesus monkeys. Rhesus No. 157 was given 3.5 c. c. of the defibrinated blood and rhesus No. 158 was given 3 c. c., both intraperitoneally.

Five-tenths cubic centimeter of the defibrinated blood were planted in a tube of standard bouillon, and during a period of observation of 12 days gave no evidence of growth.

The temperature of both animals (Nos. 157 and 158) began to rise on the ninth day after inoculation. As monkey No. 158 gave promise of a more severe reaction than monkey No. 157, the former was selected for passage.

¹ Anderson, John F., and Goldberger, Joseph: On the relation of Rocky Mountain spotted fever to the typhus fever of Mexico. A preliminary note. Public Health Reports, xxiv, Dec. 10, 1909, p. 1861.

Same. A note on the etiology of "tabardillo," the typhus fever of Mexico. Public Health Reports, xxiv, Dec. 24, 1909, p. 1941.

Same. On the infectivity of tabardillo or Mexican typhus for monkeys and studies on its mode of transmission. Public Health Reports, xxv, Feb. 4, 1910, p. 177.

Same. On the etiology of tabardillo or Mexican typhus. An experimental investigation, Journ. med. research, xxii, June, 1910, pp. 469-481.

² N.—New York series.

On the afternoon of the ninth day after inoculation, and the first day of fever, when the temperature of the animal was 41° C., monkey No. 158 was bled from the carotid artery for 50 c. c. This blood was defibrinated and a portion used for passage. Since then this infection has been carried through 11 monkey generations by inoculation of blood.

Since our case No. 1 we have seen two more cases of Brill's disease. With blood obtained from a case in the Jewish Hospital, Brooklyn, we have succeeded in infecting a rhesus monkey and effecting passage with the blood of that animal.

After intraperitoneal or intravenous inoculation there is an incubation period of 5 to 14 days. At the end of this time there is usually a rapid rise of the animal's temperature, which frequently reaches a maximum in 36 or 48 hours of 41° to 41.5° C.; the temperature remains between 40° and 41° C. until toward the end of the febrile period, when it may show a gradual decline, but almost invariably declines by crisis or rapid lysis, frequently to subnormal. After about the second day of fever the animal may show other evidences of illness, such as loss of appetite, ruffled fur, crouching posture in cage, loss of weight, and weakness. Convalescence is usually rapid. We have never noticed the presence of an eruption, although we have not searched very carefully for it. Occasionally one of a pair of animals may fail to develop the infection when inoculated with virulent blood, but on subsequent inoculation has invariably been found to be susceptible.

One attack of the infection has proved in every instance tested to have conferred immunity to infection by subsequent inoculation with virulent blood.

Having established the susceptibility of the rhesus monkey to infection by the inoculation with blood from a case of Brill's disease, it became important to determine the relationship of Brill's symptom complex to typhus fever. In order to clear up this question one of us (J. G.) proceeded to Mexico City, carrying a number of rhesus monkeys, some of which had recovered from infection with the virus obtained originally from our case No. 1 of Brill's disease, and others—fresh animals—to be used as controls.

On November 23, 1911, monkeys Nos. 95 and 133, which had recovered from an infection with the virus of Brill's disease, and control (normal) monkey No. 314, were each inoculated intravenously with 3 c. c. of defibrinated blood from rhesus No. 306. The latter animal was at this time in the third day of what appeared to have been a mild typhus reaction. During the succeeding 29 days rhesus No. 314 gave no evidence of a reaction.

On December 8, 15 days after the first inoculation, none of the three animals (Nos. 95, 133, and 314) having given any indication of a reaction, monkeys Nos. 95 and 133 were reinoculated with defibrinated blood from case No. 19-M,¹ a severe case of typhus in the sixth day of the disease (see chart No. 2). Two normal monkeys, Nos. 317 and 318, were similarly inoculated as controls. Each of these four animals was given 3.5 c. c. of the blood diluted with an equal volume of saline solution intraperitoneally.

Result.—Both control monkeys, Nos. 317 and 318, have given clear evidence of infection (see charts Nos. 3 and 4), whereas neither

¹ M—Mexican series.

Nos. 95 nor 133 has given any indication of a reaction (see charts Nos. 5 and 6).

It might be suggested that the failure of monkeys Nos. 95 and 133 to react to the second typhus inoculation was due rather to a resistance conferred by the inoculation of November 23 with the blood of rhesus No. 306 than to an immunity following the attack of Brill's disease. That this is not the case, however, is evidenced by the fact that rhesus No. 314, originally inoculated as the control for Nos. 95 and 133 in their first test, made on November 23, has since reacted promptly and sharply following a second inoculation with blood from a human case of typhus.

In order to leave no room for doubt on this point we inoculated two other monkeys (Nos. 161 and 162) that had previously reacted to an inoculation with the virus of Brill's disease. On December 29, 1911, these two animals were inoculated intraperitoneally with 6 c. c. each of defibrinated blood from a well-marked case (case 35-M) in the ninth or tenth day diluted with an equal volume of saline solution. January 1, 1912, both these animals were reinoculated with defibrinated blood from another patient (case 39-M) in the ninth day of disease, each animal receiving 4 c. c. diluted with an equal volume of saline solution intraperitoneally. Neither animal has given evidence of a reaction, although two other monkeys (Nos. 304 and 324), inoculated in precisely the same way and on the same dates, have reacted promptly and sharply.

We believe, therefore, that the conclusion is justified that an attack of Brill's disease in the monkey confers an immunity to subsequent infection with Mexican typhus (tabardillo).

Monkeys Nos. 317 and 318, which had passed through an attack of Mexican typhus fever and which had served as controls in the immunity test above described, were tested for their immunity to infection derived originally from a case of Brill's disease. These two monkeys, as well as control, were given 3 c. c. of defibrinated blood from rhesus No. 187, then in the second day of an attack of Brill's disease.

Result.—The control monkey has given a definite reaction, while neither No. 317 nor No. 318 has given any indication of a reaction. It is, therefore, permissible to conclude that Nos. 317 and 318, as a result of their attack of Mexican typhus fever, are immune to infection with Brill's disease.

SUMMARY AND CONCLUSIONS.

1. The rhesus monkey is susceptible to infection by inoculation with the blood from a case of "Brill's disease."

2. One attack of the disease in the monkey induces a definite immunity to a subsequent infection with virulent blood of the same strain.

3. Monkeys recovered from an infection with "Brill's disease" have been found to be immune to a subsequent infection with virulent blood from a case of Mexican typhus fever.

4. Monkeys recovered from an infection with Mexican typhus fever have been found to be immune to a subsequent infection with "Brill's disease."

5. From the above results we conclude that the disease described by Brill is identical with the typhus fever of Mexico, and inasmuch as the New York strain is undoubtedly of European origin, we may also conclude that the typhus of Europe and the tabardillo of Mexico are identical.

6. If this conclusion is correct, typhus fever has been present in New York City for a number of years and, according to verbal reports made to us, has occurred in other large cities of the United States.

7. These results make the clinical recognition and study of typhus fever of increased importance and necessitate the exercise of appropriate prophylactic measures.

8. It is not intended to exaggerate the menace of this disease to the public health. Nevertheless, although the disease in New York City has apparently been mild and has shown little tendency to spread, it is apparently on the increase there, and the possibility should be borne in mind that it may acquire virulence and epidemic prevalence.

We desire to express our indebtedness and to extend our thanks to Dr. Nathan E. Brill and Dr. Leo Kessel, of New York; Dr. Hiram Olsan, house physician at Mount Sinai Hospital, New York; Dr. Leon Louria, Brooklyn; and to Dr. Ellis Campus, house physician at the Jewish Hospital, Brooklyn, for the privilege of seeing cases of "Brill's disease" and obtaining material therefrom, and for many other courtesies.

For the laboratory and clinical facilities freely extended to us in Mexico City we are deeply indebted to Dr. Eduardo Licéaga, president of the superior board of health; to Dr. Octaviano Gonzalez Fabella, director of the bacteriological laboratory; to Dr. Regino Gonzalez, director of the hospital general; and to Dr. German Diaz Lombardo, director of the Hospital Juarez. We are also under many obligations to Dr. A. R. Goodman, chief surgeon of the Mexican Railways, for numerous helpful courtesies. For their kind generosity in permitting us to study their cases our thanks are due to Drs. Miguel Otero and Zenón Luna.

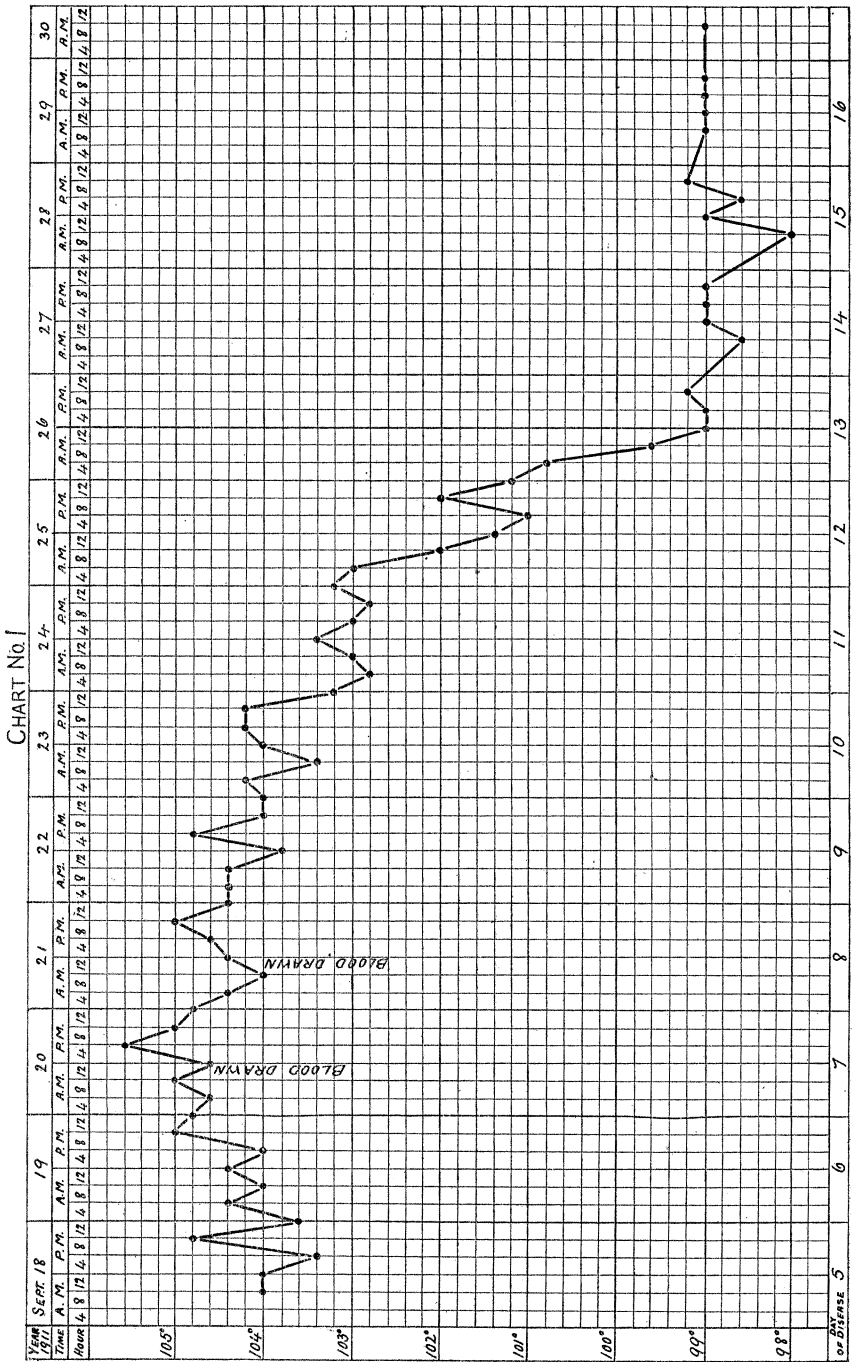


CHART NO. 1, SHOWING TEMPERATURE OF CASE NO. 1 OF "BRILL'S DISEASE."

CHART No. 2

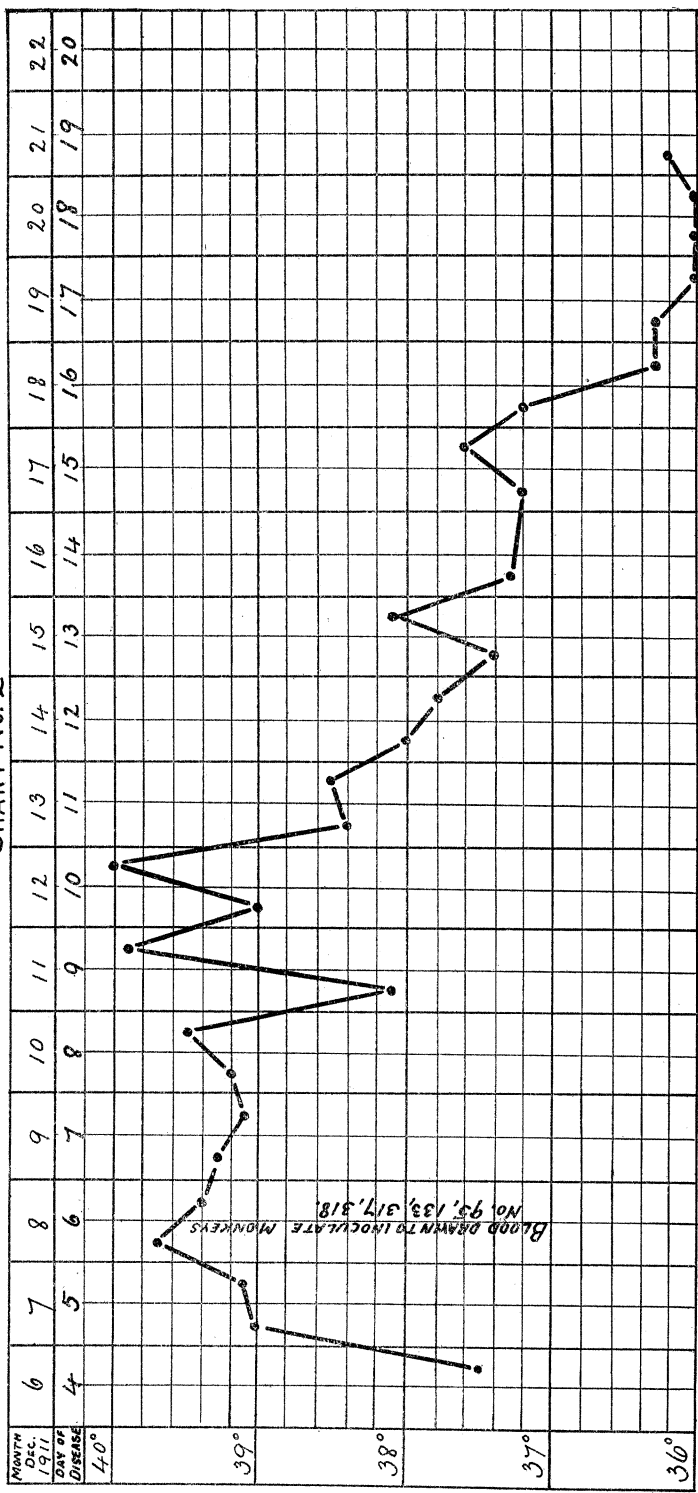


CHART NO. 2, SHOWING TEMPERATURE OF CASE NO. 19 OF TYPHUS FEVER.

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CHART No. 3

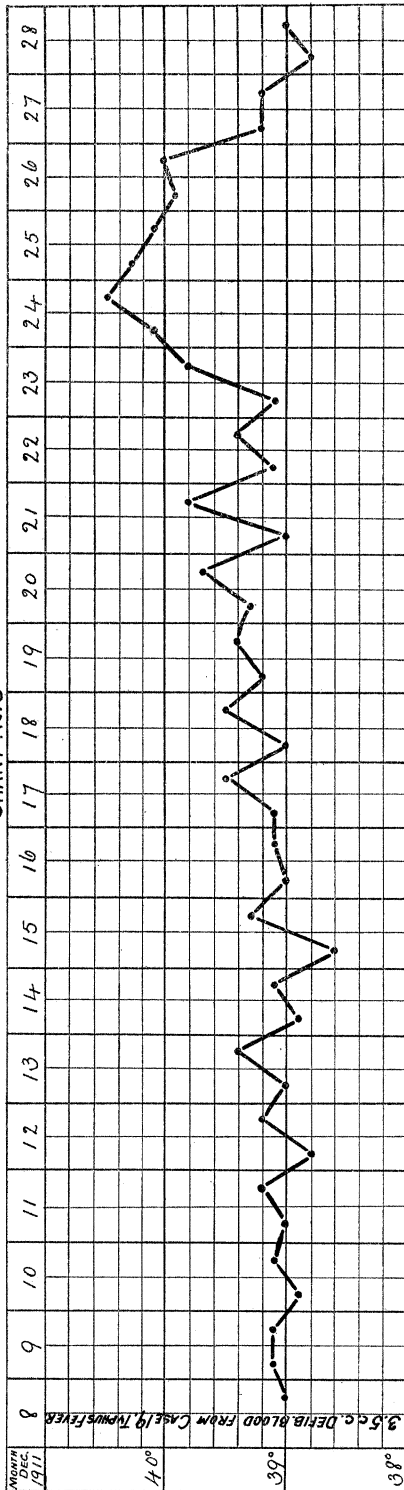


CHART NO. 3, SHOWING COURSE OF TEMPERATURE OF MONKEY NO. 317; SEE ALSO CHARTS NOS. 5 AND 6.

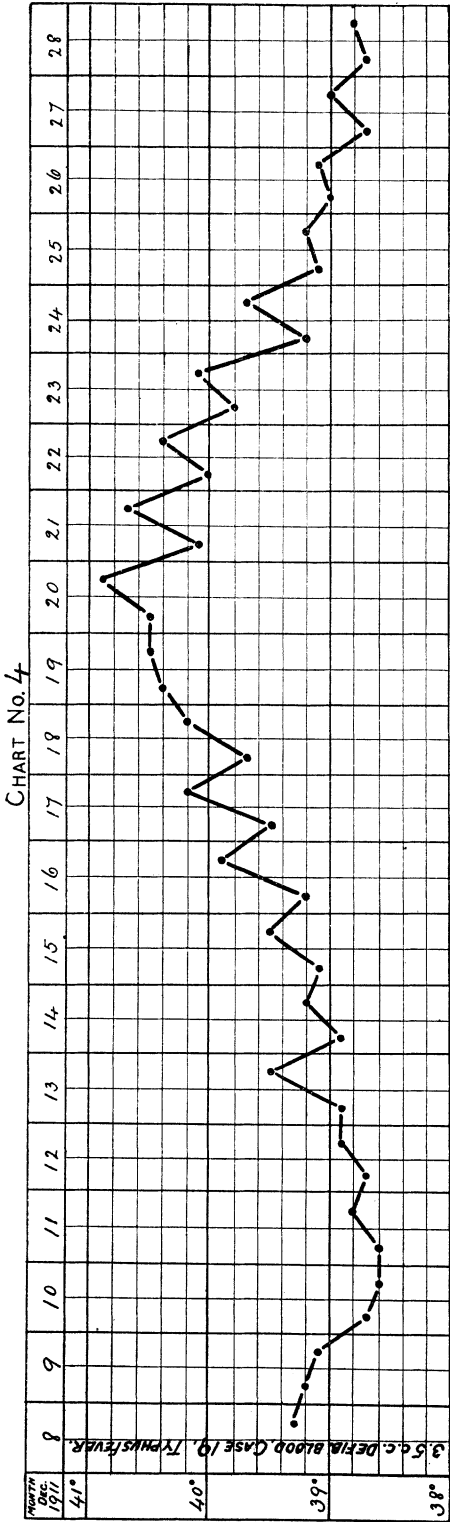


CHART NO. 4, SHOWING COURSE OF TEMPERATURE OF MONKEY NO. 318; SEE ALSO CHARTS NOS. 5 AND 6.

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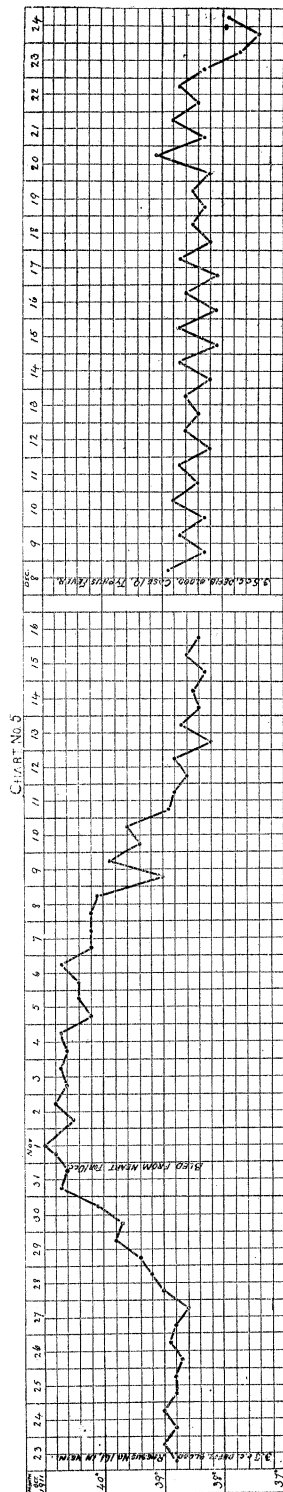


CHART NO. 5, SHOWING COURSE OF TEMPERATURE OF MONKEY NO. 95. THE CHART SHOWS THE TEMPERATURE CURVE DURING THE ATTACK OF "BRILL'S" DISEASE AND THE NEGATIVE REACTION FOLLOWING TEST OF IMMUNITY BY INJECTION OF BLOOD FROM TYPHUS FEVER CASE NO. 19; SEE ALSO CHARTS NOS. 3 AND 4.

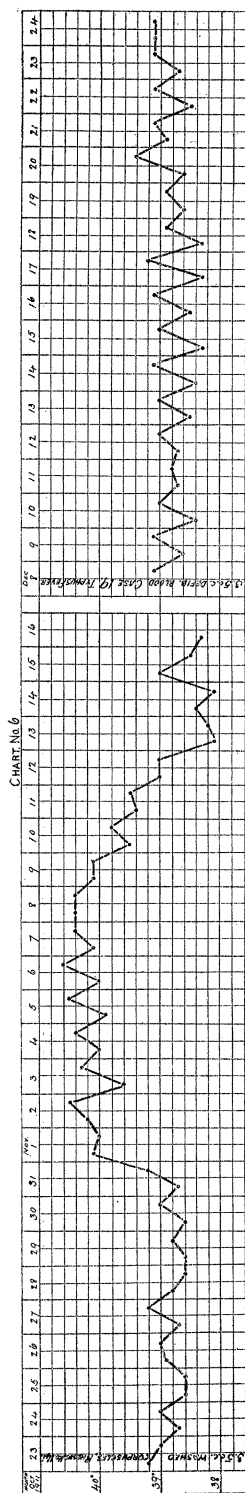


CHART NO. 6, SHOWING COURSE OF TEMPERATURE OF MONKEY NO. 133. THE CHART SHOWS THE TEMPERATURE CURVE DURING THE ATTACK OF "BRILL'S" DISEASE AND THE NEGATIVE REACTION FOLLOWING TEST OF IMMUNITY BY INJECTION OF BLOOD FROM TYPHUS FEVER CASE NO. 19; SEE ALSO CHARTS NOS. 3 AND 4.